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CO SUMMARY (WHO Report 213, www.who.int)

Carbon monoxide (CO) is a colorless, odorless gas that can be poisonous to humans. It is a product of the incomplete combustion of carbon-containing fuels and is also produced by natural processes or by biotransformation of halomethanes within the human body. With external exposure to additional carbon monoxide, subtle effects can begin to occur, and exposure to higher levels can result in death. The health effects of carbon monoxide are largely the result of the formation of carboxyhemoglobin (COHb), which impairs the oxygen carrying capacity of the blood.

1. Chemistry and analytical methods

Methods available for the measurement of carbon monoxide in ambient air range from fully automated methods using the non-disperse infrared (NDIR) technique and gas chromatography to simple semiquantitative manual methods using detector tubes. Because the formation of carboxyhemoglobin in humans is dependent on many factors, including the variability of ambient air concentrations of carbon monoxide, carboxyhemoglobin concentration should be measured rather than calculated. Several relatively simple methods are available for determining carbon monoxide by analysis either of the blood or of alveolar air that is in equilibrium with the blood. Some of these methods have been validated by careful comparative studies.

2. Sources and environmental levels of carbon monoxide in the environment

Carbon monoxide is a trace constituent of the troposphere, produced by both natural processes and human activities. Because plants can both metabolize and produce carbon monoxide, trace levels are considered a normal constituent of the natural environment. Although ambient concentrations of carbon monoxide in the vicinity of urban and industrial areas can substantially exceed global background levels, there are no reports of these currently measured levels of carbon monoxide producing any adverse effects on plants or microorganisms. Ambient concentrations of carbon monoxide, however, can be detrimental to human health and welfare, depending on the levels that occur in areas where humans live and work and on the susceptibility of exposed individuals to potentially adverse effects.
Trends in air quality data from fixed-site monitoring stations show a general decline in carbon monoxide concentrations, which reflects the efficacy of emission control systems on newer vehicles. Highway vehicle emissions in the USA account for about 50% of total emissions; non-highway transportation sources contribute 13%. The other categories of carbon monoxide emissions are other fuel combustion sources, such as steam boilers (12%); industrial processes (8%); solid waste disposal (3%); and miscellaneous other sources (14%).

Indoor concentrations of carbon monoxide are a function of outdoor concentrations, indoor sources, infiltration, ventilation and air mixing between and within rooms. In residences without sources, average carbon monoxide concentrations are approximately equal to average outdoor levels. The highest indoor carbon monoxide concentrations are associated with combustion sources and are found in enclosed parking garages, service stations and restaurants, for example. The lowest indoor carbon monoxide concentrations are found in homes, churches and health care facilities. Exposure studies show that passive cigarette smoke is associated with increasing a non-smoker's exposure by an average of about 1.7 mg/m^3 (1.5 PPM) and that use of a gas cooking range at home is associated with an increase of about 2.9 mg/m^3 (2.5 PPM). Other sources that may contribute to carbon monoxide in the home include combustion space and water heaters and coal- or wood-burning stoves.

3. Environmental distribution and transformation

Recent data on global trends in tropospheric carbon monoxide concentrations indicate a decrease over the last decade. Global background concentrations fall in the range of 60–140 $\mu g/m^3$ (50–120 ppb). Levels are higher in the Northern Hemisphere than in the Southern Hemisphere. Average background

concentrations also fluctuate seasonally. Higher levels occur in the winter months, and lower levels occur in the summer months. About 60% of the carbon monoxide found in the non-urban troposphere is attributed to human activities, both directly from combustion processes and indirectly through the oxidation of hydrocarbons and methane that, in turn, arise from agricultural activities, landfills and other similar sources. Atmospheric reactions involving carbon monoxide can produce ozone in the troposphere. Other reactions may deplete concentrations of the hydroxyl radical, a key participant in the global removal cycles of many other natural and anthropogenic trace gases, thus possibly contributing to changes in atmospheric chemistry and, ultimately, to global climate change.

4. Population exposure to carbon monoxide

During typical daily activities, people encounter carbon monoxide in a variety of microenvironments — while travelling in motor vehicles, working at their jobs, visiting urban locations associated with combustion sources, or cooking and heating with domestic gas, charcoal or wood fires — as well as in tobacco smoke. Overall, the most important carbon monoxide exposures for a majority of individuals occur in the vehicle and indoor microenvironments.

The development of small, portable electrochemical personal exposure monitors (PEMs) has made possible the measurement of carbon monoxide concentrations encountered by individuals as they move through numerous diverse indoor and outdoor microenvironments that cannot be monitored by fixed-site ambient stations. Results of both exposure monitoring in the field and modeling studies indicate that individual personal exposure determined by PEMs does not directly correlate with carbon monoxide concentrations determined by using fixed-site monitors alone. This observation is due to the mobility of people and to the spatial and temporal variability of carbon monoxide concentrations. Although they fail to show a correlation between individual personal monitor exposures and simultaneous nearest fixed-site monitor concentrations, large-scale carbon monoxide human exposure field studies do suggest that aggregate personal exposures are lower on days of lower ambient carbon monoxide levels as determined by the fixed-site monitors and higher on days of higher ambient levels. These studies point out the necessity of having personal carbon monoxide measurements to augment fixed-site ambient monitoring data when total human exposure is to be evaluated. Data from these field studies can be used to construct and test models of human exposure that account for time and activity patterns known to affect exposure to carbon monoxide.

Evaluation of human carbon monoxide exposure situations indicates that occupational exposures in some workplaces or exposures in homes with faulty or unvented combustion appliances can exceed 110 mg carbon monoxide/m^3 (100 ppm), often leading to carboxyhemoglobin levels of 10% or more with continued exposure. In contrast, the general public exposed under ambient conditions encounters such high exposure levels much less commonly. More frequently, exposures to less than 29–57 mg carbon monoxide/m^3 (25–50 ppm) for any extended period of time occur among the general population; at the low exercise levels usually engaged in under such circumstances, the resulting carboxyhemoglobin levels most typically remain 1–2% among non-smokers. These levels can be compared with the physiological norm for non-smokers, which is estimated to be in the range of 0.3–0.7% carboxyhemoglobin. In smokers, however, baseline carboxyhemoglobin concentrations average 4%, with a usual range of 3–8%, reflecting absorption of carbon monoxide from inhaled smoke.

Studies of human exposure have shown that motor vehicle exhaust is the most important source for regularly encountered elevated carbon monoxide levels. Studies indicate that the motor vehicle interior has the highest average carbon monoxide concentration (averaging 10–29 mg/m^3 [9–25 ppm]) of all microenvironments. Furthermore, commuting exposures have been shown to be highly variable, with some commuters breathing carbon monoxide in excess of 40 mg/m^3 (35 ppm).

The workplace is another important setting for carbon monoxide exposures. In general, apart from commuting to and from work, exposures at work exceed carbon monoxide exposures during non-work periods. Occupational and non-occupational exposures may overlay one another and result in a higher concentration of carbon monoxide in the blood. Most importantly, the nature of certain occupations carries an increased risk of high carbon monoxide exposure (e.g., those occupations involved directly with vehicle

driving, maintenance and parking). Occupational groups exposed to carbon monoxide from vehicle exhaust include auto mechanics; parking garage and gas station attendants; bus, truck or taxi drivers; police; and warehouse workers. Certain industrial processes can expose workers to carbon monoxide produced directly or as a by-product; they include steel production, coke ovens, carbon black production and petroleum refining. Firefighters, cooks and construction workers may also be exposed at work to high carbon monoxide levels. Occupational exposures in industries or settings with carbon monoxide production represent some of the highest individual exposures observed in field monitoring studies.

5. Toxicokinetics and mechanisms of action of carbon monoxide

Carbon monoxide is absorbed through the lungs, and the concentration of carboxyhemoglobin in the blood at any time will depend on several factors. When in equilibrium with ambient air, the carboxyhemoglobin content of the blood will depend mainly on the concentrations of inspired carbon monoxide and oxygen. However, if equilibrium has not been achieved, the carboxyhemoglobin concentration will also depend on the duration of exposure, pulmonary ventilation and the carboxyhemoglobin originally present before inhalation of the contaminated air. In addition to its reaction with hemoglobin, carbon monoxide combines with myoglobin, cytochromes and metalloenzymes such as Cytochrome c oxidase and Cytochrome P-450. The health significance of these reactions is not clearly understood but is likely to be of less importance at ambient exposure levels than that of the reaction of the gas with hemoglobin.

The exchange of carbon monoxide between the air we breathe and the human body is controlled by both physical (e.g., mass transport and diffusion) and physiological (e.g., alveolar ventilation and cardiac output) processes. Carbon monoxide is readily absorbed from the lungs into the bloodstream. The final step in this process involves competitive binding between carbon monoxide and oxygen to hemoglobin in the red blood cell, forming carboxyhemoglobin and oxyhemoglobin (O_2Hb), respectively. The binding of carbon monoxide to hemoglobin, producing carboxyhemoglobin and decreasing the oxygen carrying capacity of blood, appears to be the principal mechanism of action underlying the induction of toxic effects of low-level carbon monoxide exposures. The precise mechanisms by which toxic effects are induced via carboxyhemoglobin formation are not understood fully but likely include the induction of a hypoxic state in many tissues of diverse organ systems. Alternative or secondary mechanisms of carbon monoxide-induced toxicity (besides carboxyhemoglobin) have been hypothesized, but none has been demonstrated to operate at relatively low (near-ambient) carbon monoxide exposure levels. Blood carboxyhemoglobin levels, then, are currently accepted as representing a useful physiological marker by which to estimate internal carbon monoxide burdens due to the combined contribution of (1) endogenously derived carbon monoxide and (2) exogenously derived carbon monoxide resulting from exposure to external sources of carbon monoxide. Carboxyhemoglobin levels likely to result from particular patterns (concentrations, durations, etc.) of external carbon monoxide exposure can be estimated reasonably well from the Coburn-Forster-Kane (CFK) equation.

A unique feature of carbon monoxide exposure, therefore, is that the blood carboxyhemoglobin level represents a useful biological marker of the dose that the individual has received. The amount of carboxyhemoglobin formed is dependent on the concentration and duration of carbon monoxide exposure, exercise (which increases the amount of air inhaled per unit time), ambient temperature, health status and the characteristic metabolism of the individual exposed. The formation of carboxyhemoglobin is a reversible process; however, because of the tight binding of carbon monoxide to hemoglobin, the elimination half-time is quite long, ranging from 2 to 6.5 h, depending on the initial levels of carboxyhemoglobin and the ventilation rate of the individuals. This might lead to accumulation of carboxyhemoglobin, and even relatively low concentrations of carbon monoxide might produce substantial blood levels of carboxyhemoglobin.

The level of carboxyhemoglobin in the blood may be determined directly by blood analysis or indirectly by measuring carbon monoxide in exhaled breath. The measurement of exhaled breath has the advantages of ease, speed, and precision and greater subject acceptance than measurement of blood carboxyhemoglobin. However, the accuracy of the breath measurement procedure and the validity of the Haldane relationship between breath and blood remain in question for exposures at low environmental carbon monoxide concentrations.

Because carboxyhemoglobin measurements are not readily available in the exposed population, mathematical models have been developed to predict carboxyhemoglobin levels from known carbon monoxide exposures under a variety of circumstances. The best all-around model for carboxyhemoglobin prediction is still the equation developed by Coburn, Forster and Kane. The linear solution is useful for examining air pollution data leading to relatively low carboxyhemoglobin levels, whereas the non-linear solution shows good predictive power even for high carbon monoxide exposures. The two regression models might be useful only when the conditions of application closely approximate those under which the parameters were estimated.

Although the principal cause of carbon monoxide toxicity at low exposure levels is thought to be tissue hypoxia due to carbon monoxide binding to hemoglobin, certain physiological aspects of carbon monoxide exposure are not explained well by decreases in the intracellular oxygen partial pressure related to the presence of carboxyhemoglobin. Consequently, secondary mechanisms of carbon monoxide toxicity related to intracellular uptake of carbon monoxide have been the focus of a great deal of research interest. Carbon monoxide binding to many intracellular compounds has been well documented both *in vitro* and *in vivo*; however, it is still uncertain whether or not intracellular uptake of carbon monoxide in the presence of hemoglobin is sufficient to cause either acute organ system dysfunction or long-term health effects. The virtual absence of sensitive techniques capable of assessing intracellular carbon monoxide binding under physiological conditions has resulted in a variety of indirect approaches to the problem, as well as many negative studies.

Current knowledge pertaining to intracellular carbon monoxide binding suggests that the proteins most likely to be inhibited functionally at relevant levels of carboxyhemoglobin are myoglobin, found predominantly in heart and skeletal muscle, and Cytochrome oxidase. The physiological significance of carbon monoxide uptake by myoglobin is uncertain at this time, but sufficient concentrations of carboxymyoglobin could potentially limit the maximal oxygen uptake of exercising muscle. Although there is suggestive evidence for significant binding of carbon monoxide to Cytochrome oxidase in heart and brain tissue, it is unlikely that significant carbon monoxide binding would occur at low carboxyhemoglobin levels.

6. Health effects of exposure to carbon monoxide

The health significance of carbon monoxide in ambient air is largely due to the fact that it forms a strong bond with the hemoglobin molecule, forming carboxyhemoglobin, which impairs the oxygen carrying capacity of the blood. The dissociation of oxyhemoglobin in the tissues is also altered by the presence of carboxyhemoglobin, so that delivery of oxygen to tissues is reduced further. The affinity of human hemoglobin for carbon monoxide is roughly 240 times that for oxygen, and the proportions of carboxyhemoglobin and oxyhemoglobin formed in blood are dependent largely on the partial pressures of carbon monoxide and oxygen.

Concerns about the potential health effects of exposure to carbon monoxide have been addressed in extensive studies with both humans and various animal species. Under varied experimental protocols, considerable information has been obtained on the toxicity of carbon monoxide, its direct effects on the blood and other tissues, and the manifestations of these effects in the form of changes in organ function. Many of the animal studies, however, have been conducted at extremely high levels of carbon monoxide (i.e., levels not found in ambient air). Although severe effects from exposure to these high levels of carbon monoxide are not directly germane to the problems resulting from exposure to current ambient levels of carbon monoxide, they can provide valuable information about potential effects of accidental exposure to carbon monoxide, particularly those exposures occurring indoors.

6.1 Cardiovascular effects

Decreased oxygen uptake and the resultant decreased work capacity under maximal exercise conditions have clearly been shown to occur in healthy young adults starting at 5.0% carboxyhemoglobin, and

several studies have observed small decreases in work capacity at carboxyhemoglobin levels as low as 2.3–4.3%. These effects may have health implications for the general population in terms of potential curtailment of certain physically demanding occupational or recreational activities under circumstances of sufficiently high carbon monoxide exposure.

However, of greater concern at more typical ambient carbon monoxide exposure levels are certain cardiovascular effects (i.e., aggravation of angina symptoms during exercise) likely to occur in a smaller, but sizeable, segment of the general population. This group, chronic angina patients, is currently viewed as the most sensitive risk group for carbon monoxide exposure effects, based on evidence for aggravation of angina occurring in patients at carboxyhemoglobin levels of 2.9–4.5%. Dose–response relationships for cardiovascular effects in coronary artery disease patients remain to be defined more conclusively, and the possibility cannot be ruled out at this time that such effects may occur at levels below 2.9% carboxyhemoglobin. Therefore, new published studies are evaluated in this document to determine the effects of carbon monoxide on aggravation of angina at levels in the range of 2–6% carboxyhemoglobin.

Five key studies have investigated the potential for carbon monoxide exposure to enhance the development of myocardial ischemia during exercise in patients with coronary artery disease. An early study found that exercise duration was significantly decreased by the onset of chest pain (angina) in patients with angina pectoris at post-exposure carboxyhemoglobin levels as low as 2.9%, representing an increase of 1.6% carboxyhemoglobin over the baseline. Results of a large multi-center study demonstrated effects in patients with reproducible exercise-induced angina at post-exposure carboxyhemoglobin levels of 3.2%, corresponding to an increase of 2.0% carboxyhemoglobin from the baseline. Others also found similar effects in patients with obstructive coronary artery disease and evidence of exercise-induced ischemia at post-exposure carboxyhemoglobin levels of 4.1% and 5.9%, respectively, representing increases of 2.2% and 4.2% carboxyhemoglobin over the baseline. One study of subjects with angina found an effect at 3% carboxyhemoglobin, representing an increase of 1.5% carboxyhemoglobin from the baseline. Thus, the lowest-observed-adverse-effect level in patients with exercise-induced ischemia is somewhere between 3% and 4% carboxyhemoglobin, representing an increase of 1.5–2.2% carboxyhemoglobins from the baseline. Effects on silent ischemia episodes, which represent the majority of episodes in these patients, have not been studied.

The adverse health consequences of low-level carbon monoxide exposure in patients with ischemic heart disease are very difficult to predict in the at-risk population of individuals with heart disease. Exposure to carbon monoxide that is sufficient to achieve 6% carboxyhemoglobin, but not lower levels of carboxyhemoglobin, has been shown to significantly increase the number and complexity of exercise-induced arrhythmia in patients with coronary artery disease and baseline ectopy. This finding, combined with the time-series studies of carbon monoxide-related morbidity and mortality and the epidemiological work of tunnel workers who are routinely exposed to automobile exhaust, is suggestive but not conclusive evidence that carbon monoxide exposure may provide an increased risk of sudden death from arrhythmia in patients with coronary artery disease.

Previous assessments of the cardiovascular effects of carbon monoxide have identified what appears to be a linear relationship between the level of carboxyhemoglobin in the blood and decrements in human maximal exercise performance, measured as maximal oxygen uptake. Exercise performance consistently decreases at a blood level of about 5% carboxyhemoglobin in young, healthy, non-smoking individuals. Some studies have even observed a decrease in short-term maximal exercise duration at levels as low as 2.3–4.3% carboxyhemoglobin; however, this decrease is so small as to be of concern mainly for competing athletes rather than for ordinary people conducting the activities of daily life.

There is also evidence from both theoretical considerations and experimental studies in laboratory animals that carbon monoxide can adversely affect the cardiovascular system, depending on the exposure conditions utilized in these studies. Although disturbances in cardiac rhythm and conduction have been noted in healthy and cardiac-impaired animals, results from these studies are not conclusive. The lowest level at which effects have been observed varies, depending upon the exposure regime used and species tested. Results from animal studies also indicate that inhaled carbon monoxide can increase hemoglobin concentration and hematocrit ratio, which probably represents a compensation for the

reduction in oxygen transport caused by carbon monoxide. At high carbon monoxide concentrations, excessive increases in hemoglobin and hematocrit may impose an additional workload on the heart and compromise blood flow to the tissues.

There is conflicting evidence that carbon monoxide exposure will enhance development of atherosclerosis in laboratory animals, and most studies show no measurable effect. Similarly, the possibility that carbon monoxide will promote significant changes in lipid metabolism that might accelerate atherosclerosis is suggested in only a few studies. Any such effect must be subtle, at most. Finally, carbon monoxide probably inhibits rather than promotes platelet aggregation. In general, there are few data to indicate that an atherogenic effect of exposure would be likely to occur in human populations at commonly encountered levels of ambient carbon monoxide.

6.2 Acute pulmonary effects

It is unlikely that carbon monoxide has any direct effects on lung tissue except for extremely high concentrations associated with carbon monoxide poisoning. Human studies on the effects of carbon monoxide on pulmonary function are complicated by the lack of adequate exposure information, the small number of subjects studied and the short exposures explored. Occupational or accidental exposure to the products of combustion and pyrolysis, particularly indoors, may lead to acute decrements in lung function if the carboxyhemoglobin levels are high. It is difficult, however, to separate the potential effects of carbon monoxide from those due to other respiratory irritants in the smoke and exhaust. Community population studies on carbon monoxide in ambient air have not found any significant relationship with pulmonary function, symptomatology and disease.

6.3 Cerebrovascular and behavioral effects

No reliable evidence demonstrating decrements in neurobehavioral function in healthy, young adults has been reported at carboxyhemoglobin levels below 5%. Results of studies conducted at or above 5% carboxyhemoglobin are equivocal. Much of the research at 5% carboxyhemoglobin did not show any effect even when behaviors similar to those affected in other studies at higher carboxyhemoglobin levels were involved. However, investigators failing to find carbon monoxide-related neurobehavioral decrements at 5% or higher carboxyhemoglobin levels may have utilized tests not sufficiently sensitive to reliably detect small effects of carbon monoxide. From the empirical evidence, then, it can be said that carboxyhemoglobin levels greater than or equal to 5% may produce decrements in neurobehavioral function. It cannot be said confidently, however, that carboxyhemoglobin levels lower than 5% would be without effect. However, only young, healthy adults have been studied using demonstrably sensitive tests and carboxyhemoglobin levels of 5% or greater. The question of groups at special risk for neurobehavioral effects of carbon monoxide, therefore, has not been explored.

Of special note are those individuals who are taking drugs with primary or secondary depressant effects that would be expected to exacerbate carbon monoxide-related neurobehavioral decrements. Other groups at possibly increased risk for carbon monoxide-induced neurobehavioral effects are the aged and ill, but these groups have not been evaluated for such risk.

Under normal circumstances, the brain can increase blood flow or tissue oxygen extraction to compensate for the hypoxia caused by exposure to carbon monoxide. The overall responses of the cerebrovasculature are similar in the fetus, newborn and adult animal; however, the mechanism of the increase in cerebral blood flow is still unclear. In fact, several mechanisms working simultaneously to increase blood flow appear likely, and these may involve metabolic and neural aspects as well as the oxyhemoglobin dissociation curve, tissue oxygen levels and even a histotoxic effect of carbon monoxide. Whether these compensatory mechanisms will continue to operate successfully in a variety of conditions where the brain or its vasculature are compromised (i.e., stroke, head injury, atherosclerosis, hypertension) is also unknown. Aging increases the probability of such injury and disease. It is also possible that there exist individual differences with regard to carboxyhemoglobin sensitivity and compensatory mechanisms.

Behaviors that require sustained attention or sustained performance are most sensitive to disruption by carboxyhemoglobin. The group of human studies on hand–eye coordination (compensatory tracking), detection of infrequent events (vigilance) and continuous performance offers the most consistent and defensible evidence of carboxyhemoglobin effects on behavior at levels as low as 5%. These effects at low carbon monoxide exposure concentrations, however, have been very small and somewhat controversial. Nevertheless, the potential consequences of a lapse of coordination and vigilance on the continuous performance of critical tasks by operators of machinery such as public transportation vehicles could be serious.

6.4 Developmental toxicity

Studies in several laboratory animal species provide strong evidence that maternal carbon monoxide exposures of 170–230 mg/m^3 (150–200 ppm), leading to approximately 15–25% carboxyhemoglobin, produce reductions in birth weight, cardiomegaly, delays in behavioral development and disruption in cognitive function. Isolated experiments suggest that some of these effects may be present at concentrations as low as 69–74 mg/m^3 (60–65 ppm; approximately 6–11% carboxyhemoglobin) maintained throughout gestation. Studies relating human carbon monoxide exposure from ambient sources or cigarette smoking to reduced birth weight are of concern because of the risk for developmental disorders; however, many of these studies have not considered all sources of carbon monoxide. The current data from children suggesting a link between environmental carbon monoxide exposures and sudden infant death syndrome are weak.

6.5 Other systemic effects

Laboratory animal studies suggest that enzyme metabolism of xenobiotic compounds may be affected by carbon monoxide exposure. Most of the authors of these studies have concluded, however, that effects on metabolism at low carboxyhemoglobin levels (15%) are attributable entirely to tissue hypoxia produced by increased levels of carboxyhemoglobin, because they are no greater than the effects produced by comparable levels of hypoxic hypoxia. At higher levels of exposure, where carboxyhemoglobin concentrations exceed 15–20%, carbon monoxide may directly inhibit the activity of mixed-function oxidases. The decreases in xenobiotic metabolism shown with carbon monoxide exposure might be important to individuals receiving treatment with drugs.

Inhalation of high levels of carbon monoxide, leading to carboxyhemoglobin concentrations greater than 10–15%, has been reported to cause a number of other systemic effects in laboratory animals, as well as effects in humans suffering from acute carbon monoxide poisoning. Tissues of highly active oxygen metabolism, such as heart, brain, liver, kidney and muscle, may be particularly sensitive to carbon monoxide poisoning. The effects of high levels of carbon monoxide on other tissues are not as well known and are, therefore, less certain. There are reports in the literature of effects on liver, kidney, bone and the immune capacity of the lung and spleen. It is generally agreed that the severe tissue damage occurring during acute carbon monoxide poisoning is due to one or more of the following: (1) ischemia resulting from the formation of carboxyhemoglobin, (2) inhibition of oxygen release from oxyhemoglobin, (3) inhibition of cellular Cytochrome function (e.g., Cytochrome oxidases) and (4) metabolic acidosis.

Only relatively weak evidence points towards possible carbon monoxide effects on fibrinolytic activity, and then only at rather high carbon monoxide exposure levels. Similarly, whereas certain data also suggest that perinatal effects (e.g., reduced birth weight, slowed postnatal development, sudden infant death syndrome) are associated with carbon monoxide exposure, insufficient evidence exists by which to either qualitatively confirm such an association in humans or establish any pertinent exposure–effect relationships.

6.6 Adaptation

The only evidence for short- or long-term compensation for or adaptation to increased carboxyhemoglobin levels in the blood is indirect. Experimental animal data indicate that increased carboxyhemoglobin levels produce physiological responses that tend to offset other deleterious effects of carbon monoxide exposure. Such responses are (1) increased coronary blood flow, (2) increased cerebral blood flow, (3)

increased hemoglobin through increased haematopoiesis and (4) increased oxygen consumption in muscle.

Short-term compensatory responses in blood flow or oxygen consumption may not be complete or might even be lacking in certain persons. For example, it is known from laboratory animal studies that coronary blood flow increases with increasing carboxyhemoglobin, and it is known from human clinical studies that subjects with ischemic heart disease respond to the lowest levels of carboxyhemoglobin (6% or less). The implication is that in some cases of cardiac impairment, the short-term compensatory mechanism is impaired.

From neurobehavioral studies, it is apparent that decrements due to carbon monoxide have not occurred consistently in all subjects, or even in the same studies, and have not demonstrated a dose–response relationship with increasing carboxyhemoglobin levels. The implication from these data is that there might be some threshold or time lag in a compensatory mechanism such as increased blood flow. Without direct physiological evidence in either laboratory animals or, preferably, humans, this concept can only be hypothesized.

The mechanism by which long-term adaptation would occur, if it could be demonstrated in humans, is assumed to be an increased hemoglobin concentration via an increase in haematopoiesis. This alteration in hemoglobin production has been demonstrated repeatedly in laboratory animal studies, but no recent studies have been conducted indicating or suggesting that some adaptational benefit has occurred or would occur. Furthermore, even if the hemoglobin increase is a signature of adaptation, it has not been demonstrated to occur at low ambient concentrations of carbon monoxide.

7. Combined exposure of carbon monoxide with altitude, drugs and other air pollutants and environmental factors

7.1 High-altitude effects

Although there are many studies comparing and contrasting the effects of inhaling carbon monoxide with those produced by exposure to altitude, there are relatively few reports on the combined effects of inhaling carbon monoxide at altitude. There are data to support the possibility that the effects of these two hypoxia episodes are at least additive. These data were obtained at carbon monoxide concentrations that are too high to have much significance for regulatory concerns.

There are even fewer studies of the long-term effects of carbon monoxide at high altitude. These studies indicate few changes at carbon monoxide concentrations below 110 mg/m^3 (100 ppm) and altitudes below 4570 m. the fetus, however, may be particularly sensitive to the effects of carbon monoxide at altitude; this is especially true with the high levels of carbon monoxide associated with maternal smoking.

7.2 Carbon monoxide interaction with drugs

There remains little direct information on the possible enhancement of carbon monoxide toxicity by concomitant drug use or abuse; however, there are some data suggesting cause for concern. There is some evidence that interactions between drug effects and carbon monoxide exposure can occur in both directions; that is, carbon monoxide toxicity may be enhanced by drug use, and the toxic or other effects of drugs may be altered by carbon monoxide exposure. Nearly all the published data that are available on carbon monoxide combinations with drugs concern the use of alcohol.

The use and abuse of psychoactive drugs and alcohol are ubiquitous in society. Because of the effect of carbon monoxide on brain function, interactions between carbon monoxide and psychoactive drugs could be anticipated. Unfortunately, little systematic research has addressed this question. In addition, little of the research that has been done has utilized models for expected effects from treatment combinations. Thus, it is often not possible to assess whether the combined effects of drugs and carbon monoxide exposure are additive or differ from additivity. It is important to recognize that even additive effects of combinations can be of clinical significance, especially when the individual is unaware of the combined

hazard. The greatest evidence for a potentially important interaction of carbon monoxide comes from studies with alcohol in both laboratory animals and humans, where at least additive effects have been obtained. The significance of this is augmented by the high probable incidence of combined alcohol use and carbon monoxide exposure.

7.3 Combined exposure of carbon monoxide with other air pollutants and environmental factors

Many of the data concerning the combined effects of carbon monoxide and other pollutants found in the ambient air are based on laboratory animal experiments. Only a few human studies are available. Early studies in healthy human subjects on common air pollutants such as carbon monoxide, nitrogen dioxide, ozone or peroxyacetyl nitrate failed to show any interaction from combined exposure. In laboratory studies, no interaction was observed following combined exposure to carbon monoxide and common ambient air pollutants such as nitrogen dioxide or sulfur dioxide. However, an additive effect was observed following combined exposure to high levels of carbon monoxide and nitric oxide, and a synergistic effect was observed after combined exposure to carbon monoxide and ozone.

Toxicological interactions of combustion products, primarily carbon monoxide, carbon dioxide and hydrogen cyanide, at levels typically produced by indoor and outdoor fires have shown a synergistic effect following carbon monoxide plus carbon dioxide exposure and an additive effect with hydrogen cyanide. Additive effects were also observed when carbon monoxide, hydrogen cyanide and low oxygen were combined; adding carbon dioxide to this combination was synergistic.

Finally, studies suggest that environmental factors such as heat stress and noise may be important determinants of health effects when combined with exposure to carbon monoxide. Of the effects described, the one potentially most relevant to typical human exposures is a greater decrement in the exercise performance seen when heat stress is combined with 57 mg carbon monoxide/m^3 (50 ppm).

7.4 Tobacco smoke

Besides being a source of carbon monoxide for smokers as well as non-smokers, tobacco smoke is also a source of other chemicals with which environmental carbon monoxide could interact. Available data strongly suggest that acute and chronic carbon monoxide exposure attributed to tobacco smoke can affect the cardiopulmonary system, but the potential interaction of carbon monoxide with other products of tobacco smoke confounds the results. In addition, it is not clear if incremental increases in carboxyhemoglobin caused by environmental exposure would actually be additive to chronically elevated carboxyhemoglobin levels due to tobacco smoke, because some physiological adaptation may take place.

8. Evaluation of subpopulations potentially at risk from carbon monoxide exposure

Most information on the health effects of carbon monoxide involves two carefully defined population groups — young, healthy adults and patients with diagnosed coronary artery disease. On the basis of the known effects described, patients with reproducible exercise-induced ischemia appear to be best established as a sensitive group within the general population that is at increased risk for experiencing health effects of concern (i.e., decreased exercise duration due to exacerbation of cardiovascular symptoms) at ambient or near-ambient carbon monoxide exposure concentrations that result in carboxyhemoglobin levels down to 3%. A smaller sensitive group of healthy individuals experiences decreased exercise duration at similar levels of carbon monoxide exposure, but only during short-term maximal exercise. Decrements in exercise duration in the healthy population would therefore be of concern mainly to competing athletes, rather than to ordinary people carrying out the common activities of daily life.

It can be hypothesized, however, from both clinical and theoretical work and from experimental research on laboratory animals, that certain other groups in the population may be at probable risk from exposure to carbon monoxide. Identifiable probable risk groups can be categorized by gender differences; by age (e.g., fetuses, young infants and the elderly); by genetic variations (i.e., hemoglobin abnormalities); by pre-

existing diseases, either known or unknown, that already decrease the availability of oxygen to critical tissues; or by the use of medications, recreational drugs or alterations in environment (e.g., exposure to other air pollutants or to high altitude). Unfortunately, little empirical evidence is currently available by which to specify health effects associated with ambient or near-ambient carbon monoxide exposures for most of these probable risk groups.

9. Carbon monoxide poisoning

Most of this document is concerned with the relatively low concentrations of carbon monoxide that induce effects in humans at, or near, the lower margin of carboxyhemoglobin detection by current medical technology. Yet health effects associated with exposure to this pollutant range from the more subtle cardiovascular and neurobehavioral effects at low ambient concentrations to unconsciousness and death after acute exposure to high concentrations of carbon monoxide. The morbidity and mortality resulting from the latter exposures can be a significant public health concern.

Carbon monoxide is responsible for a large percentage of the accidental poisonings and deaths reported throughout the world each year. Certain conditions exist in both the indoor and outdoor environments that cause a small percentage of the population to become exposed to dangerous levels of carbon monoxide. Outdoors, concentrations of carbon monoxide are highest near street intersections, in congested traffic, near exhaust gases from internal combustion engines and from industrial sources, and in poorly ventilated areas such as parking garages and tunnels. Indoors, carbon monoxide concentrations are highest in workplaces or in homes that have faulty or poorly vented combustion appliances or downdrafts or backdrafts.

The symptoms and signs of acute carbon monoxide poisoning correlate poorly with the level of carboxyhemoglobin measured at the time of arrival at the hospital. Carboxyhemoglobin levels below 10% are usually not associated with symptoms. At higher carboxyhemoglobin saturations of 10–30%, neurological symptoms of carbon monoxide poisoning can occur, such as headache, dizziness, weakness, nausea, confusion, disorientation and visual disturbances. Exertional dyspnea, increases in pulse and respiratory rates and syncope are observed with continuous exposure, producing carboxyhemoglobin levels from 30% to 50%. When carboxyhemoglobin levels are higher than 50%, coma, convulsions and cardiopulmonary arrest may occur.

Complications occur frequently in carbon monoxide poisoning (immediate death, myocardial impairment, hypotension, arrhythmia's, pulmonary oedema). Perhaps the most insidious effect of carbon monoxide poisoning is the delayed development of neuropsychiatric impairment within 1–3 weeks and the neurobehavioral consequences, especially in children. Carbon monoxide poisoning during pregnancy results in high risk for the mother, by increasing the short-term complications rate, and for the fetus, by causing fetal death, developmental disorders and cerebral anoxic lesions. Furthermore, the severity of fatal intoxication cannot be assessed by the maternal rate.

Carbon monoxide poisoning occurs frequently, has severe consequences, including immediate death, involves complications and late sequelae and is often overlooked. Efforts in prevention and in public and medical education should be encouraged.

10. Recommended WHO guidelines

The following guideline values (ppm values rounded) and periods of time-weighted average exposures have been determined in such a way that the carboxyhemoglobin level of 2.5% is not exceeded, even when a normal subject engages in light or moderate exercise:

100mg/m^3(87ppm)for15min
60mg/m^3(52ppm)for30min

30	26	1	(35 ppm x1° if exercising '89 US Ambient Ambient Std)
10	9	8 (EPA 2000)	(NIOSH '93 40 x8°) (OSHA '89 50ppm x8°occup)